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(54) Title: METHODS FOR MODULATING AN IMMUNE RESPONSE BY MODULATING KRC ACTIVITY

(57) **Abstract:** This invention demonstrates that KRC molecules have multiple important functions as modulating agents in regulating a wide variety of cellular processes including: inhibiting NFkB transactivation, increasing TNF-alpha induced apoptosis, inhibiting JNK activation, inhibiting endogenous TNF-alpha expression, promoting immune cell proliferation and immune cell activation (*e.g.*, in Th1 cells and/or Th2), activating IL-2 expression *e.g.*, by activating the AP-1 transcription factor, and increasing actin polymerization. The present invention also demonstrates that KRC interacts with TRAF. Furthermore, the present invention demonstrates that KRC physically interacts with the c-Jun component of AP-1 to control its degradation. The present invention also demonstrates that KRC is downstream of several lymphocyte membrane receptors, including TNFR, TCR and TGFβR. Upon TNFR signaling, KRC associates with the adaptor protein TRAF2 to inhibit NFkB and JNK-dependent gene expression. Upon TCR stimulation, KRC expression is rapidly induced and KRC physically associates with the c-Jun transcription factor to augment AP-1 dependent gene transcription. KRC knock-out (KO) T cells have impaired production of AP-1-dependent genes such as CD69 and IL-2. Upon TCR stimulation KRC also associates with the Th2-specific transcription factor GATA3, and T cells lacking KRC have impaired production of GATA3 dependent Th2 cytokines, IL-4, IL-5 and IL- 13. Finally, upon TGFβ receptor signaling, KRC physically associates with the transcription factor SMAD3 to activate IgA germline transcription in B cells, since KRC KO B cells have impaired IgA production and germline Iga (GLα) gene transcription. Methods for identifying modulators of KRC activity are provided. Methods for modulating an immune response and KRC-associated disorders using agents that modulate KRC expression and/or activity are also provided.

WO 2005/042726 A2